Prognosis in Women with Interval Breast Cancer: Population Based Observational Cohort Study

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RESEARCH

Prognosis in women with interval breast cancer: population based observational cohort study


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Abstract

Objective To compare the prognosis in women with interval breast cancer (cancer detected after a normal screening mammogram and before the next scheduled mammogram) with breast cancer detected among women not yet invited to mammography screening (non-screened).

Design Population based observational study.

Setting Norwegian breast cancer screening programme, implemented in different counties from 1996 to 2005.

Participants 7116 women with a diagnosis of breast cancer at age 50 to 72 years; 1816 had interval breast cancer and 5300 had a diagnosis of breast cancer but had not yet been invited to screening.

Main outcome measures Characteristics of the breast tumours, and survival of the women using Kaplan Meier curves and multivariable Cox proportional hazard models.

Results Although interval cancers on average were slightly larger than the cancers in women not invited to screening, the histological type or status of axilliary lymph nodes did not differ noticeably between the two groups. Among interval cancers, there were no appreciable trends in size, nodal status, grade, or hormone receptor positivity associated with time since the last normal mammogram as a marker of growth rate. After 10 years of follow-up, the survival rates were 79.1% (95% confidence interval 75.4% to 82.3%) among women with interval cancers and 76.8% (75.3% to 78.2%) among women in the non-screened cancer group (hazard ratio 0.98, 95% confidence interval 0.84 to 1.15; P=0.53). Analyses stratified by time since last normal mammogram, age at diagnosis, or screening round showed similar results.

Conclusion The prognosis of women with interval breast cancers was the same as that of women with breast cancers diagnosed without mammography screening.

Introduction

When mammography screening programmes are fully implemented, interval cancers comprise a substantial proportion of incident breast cancers. Interval cancers may have been overlooked at the last mammography examination or become apparent because they grew so rapidly that the detectable preclinical phase (sojourn time) was shorter than the screening interval.

Because interval breast cancers in some studies on average are larger,[1 2] of a more advanced stage,[1] and express proliferative markers more than screen detected tumours,[1 3] it has been suggested that prognosis of interval breast cancers is poorer than that of screen detected breast cancers.[3] However, prognostic studies may be misleading when comparing interval breast cancers with screen detected breast cancers because the screen detected breast cancers are affected by length bias sampling, lead time bias, and overdiagnosis bias. Therefore the valid comparison group for assessment of prognosis in women with interval breast cancers is non-screen detected cancers among women not invited to mammography screening, which are unaffected by the biases that screening entails. Comparisons with historical groups, as in many previous studies, may also lead to confounding because survival from breast cancer has improved over time.[4 5] Only a few, small studies have compared the survival of women with interval breast cancer with those with non-screen detected breast cancer, with inconsistent findings.[6-13]

In this population based study we took advantage of the nationwide breast cancer screening programme in Norway, which has been gradually implemented over a nine year period.[13] This staggered roll out allowed a comparison between women with interval breast cancer and those with breast cancer

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diagnosed within the same period but before they had been invited to mammography screening.

We investigated whether breast cancers detected in the interval after a normal mammography screening result but before the next scheduled screening are more lethal and thus may need more aggressive treatment than non-screen detected breast cancers.

Methods

Breast cancer screening programme

Since 1951, reporting of cancer diagnoses to the nationwide Cancer Registry of Norway has been compulsory by national legislation. Patients are identified in the registry by their unique national registration number, assigned to all residents in Norway and including date of birth. The cancer registry has maintained nearly 100% completeness for solid cancers, including breast cancer.[14 15]

In 1996 the Norwegian breast cancer screening programme started in four counties and then expanded gradually, county by county, over the course of nine years.[4 13] Since 2005, all women in Norway aged 50-69 years are invited to mammography screening every two years. The Central Population Register of Norway identifies women eligible for screening by their national registration number. Invitations are posted to each eligible woman, suggesting an appointment time.[16] Two radiologists independently read two view mammograms (craniocaudal views and mediolateral oblique views) in accordance with European guidelines for quality assurance,[17] which are classified according to a five point interpretation scale reflecting the probability of cancer.[18] The decision as to whether further diagnostic examinations are necessary is based on the consensus of two experienced radiologists. After this final decision, no further diagnostic tests are done before the next scheduled screening invitation.

For the purpose of the study we classified women as having interval cancer if breast cancer was diagnosed within two years and two months of the last normal screening mammogram but before invitation to the next screening. Hence the cohort of women with interval cancers included only those who were invited participants in the screening programme but had non-screened detected breast cancer. For the present analysis we extended the screening interval by two months because we retrieved date of diagnosis from two databases that were not completely in agreement about the date; the additional two months made it possible to include all women classified as having interval cancers in the screening database. Among women who reach the upper age limit of 70 years for invitation to screening, we defined interval cancers as those diagnosed within two years and two months after the last normal screening examination.

We further divided the cancers into groups (six month intervals) according to the time between the date of diagnosis and the date of the last normal screening examination, to explore the hypothesis that more rapidly growing cancers arising shortly after a normal screening mammogram have a poorer prognosis.[8 19 20] Owing to increased experience by the radiologists, screening sensitivity might increase with increasing screening rounds. Under this assumption the number of cancers overlooked at screening mammography should decline with time since start of the screening programme. Thus a growing proportion of cancers detected between scheduled screenings should be true interval cancers. If true interval cancers were a more aggressive subtype of breast cancers, in theory the survival of women with these tumours might be worse than for those whose breast cancer is overlooked, and with increasing screening rounds and more experience the prognosis would be worse. We therefore carried out a secondary analysis restricted to interval breast cancers stratified by screening round.

Study population

From the cancer registry database we retrieved information on date of diagnosis, age at diagnosis, county of residency, classification of the cancer according to the pathological tumour, node, metastases (pTNM) classification (International Union Against Cancer guidelines),[21] and tumour stage in all women with a first diagnosis of invasive breast cancer at age 50 to 72 years in Norway between 1 January 1996 and 31 December 2006. The stage of breast tumour is coded as I (localised cancer), II (regional cancer), III (cancer fixed to the skin or the chest wall), or IV (cancer with distant metastases). To determine whether a diagnosis was made before or after invitation to screening we linked data on all the women to the screening database at the cancer registry. We then further categorised women with breast cancer diagnosed after invitations to screening as interval cancers if they met our criteria.

From the screening database we further retrieved data on tumour grade (based on the Nottingham grading system, I-III[22]); oestrogen and progesterone receptor status[21]; pTNM classification; and dates of invitation and attendance to the screening programme. We classified oestrogen and progesterone receptors as positive (≥10% positive staining) or negative (<10% positive staining). These data were not available from the registry's database and as a result are not available for women not invited to mammography screening. We defined screening rounds by county rather than by individual women. The follow-up period was from 1 January 1996 to 31 December 2006. Linkage to the Central Population Register of Norway and the National Death Register allowed censoring at date of emigration or death. For the purpose of this study we defined two study cohorts:

- *Interval cancer group*—comprising all women with a first diagnosis of invasive breast cancer during the interval between two screening rounds or breast cancer diagnosed within two years and two months after the date of the last normal examination in the breast cancer screening programme between 1996 and 2006.
- *Non-screened cancer group*—comprising all women with a first diagnosis of invasive breast cancer who had not yet been invited to the breast cancer screening programme between 1996 and 2006.

Statistical analyses

We used the Pearson χ^2 test to compare the interval cancer group with the non-screened cancer group according to the characteristics of the tumours, and we used a linear regression model to test trends across time intervals from a last normal screening result. Using life table techniques we calculated breast cancer specific survival rates and overall survival rates, illustrated by Kaplan-Meier plots, and we compared these rates using the log rank test. Censoring occurred at date of emigration, date of death from causes other than breast cancer, or the end of the follow-up period (31 December 2006), whichever came first.

Hazard ratios were calculated using Cox proportional hazard models. We used likelihood ratio statistics to compare groups. We adjusted for age at diagnosis by four categories: 50-54, 55-59, 60-64, and 65-72 years. We further adjusted for time

trends, county of residence, and time since last normal screening result. Because survival from breast cancer differed between counties, we adjusted for county and time trends by including county specific trend variables in the model.[4] We did not adjust for stage at diagnosis owing to the likelihood of stage migration,[23] but we carried out further analyses stratified by stage. For interval cancers only, we carried out secondary analyses to examine the association and possible interaction of time since last normal screening result and screening round. The proportional hazards assumption was tested by both graphical methods and Schoenfeld residuals and it was achieved.

All test statistics were two tailed, and we considered P values <0.05 to be significant. Calculations were done with the statistical package Stata 10.0.

Results

Table 1⇓ summarises the characteristics of the 1816 women in the interval cancer group and the 5300 women in the non-screened cancer group. The mean age at diagnosis was similar between the groups, whereas the mean follow-up time was 3.6 (SD 2.6, maximum 10.6) years for the interval cancer group and 6.3 (SD 3.0, maximum 11.2) years for the non-screened cancer group. Compared with the non-screened cancer group, the interval cancer group had a slightly higher proportion of lobular cancers, large tumours (>20 mm diameter), negative axillary lymph nodes, and stage II rather than stage I disease (table 1). The proportion of women who had a sentinel node biopsy was about three times higher in the interval cancer group than in the non-screened cancer group. Adjuvant tamoxifen was given to 701 (38.6%) of the women in the interval cancer group and 1912 (36.1%) in the non-screened cancer group.

Table 2⇓ shows the characteristics of interval breast cancers by six month intervals from date of the last normal screening result. The number of interval cancers increased with increasing time after a normal result. The mean tumour diameter for interval cancers increased by only 2.2 mm during the two years after a normal screening result (P for trend 0.03). There was no evidence that any other tumour characteristics varied by time since last normal screening result. The results were essentially the same with shorter intervals (data not shown).

Cumulative breast cancer survival did not differ between the two groups (P=0.53, fig 1⇓). After 10 years of follow-up, the survival rate among women with interval cancers was 79.1% (95% confidence interval 75.4% to 82.3%) and among women with cancers in the non-screened group was 76.8% (75.3% to 78.2%). Five year and 10 year age adjusted survival estimates by tumour stage at diagnosis were also similar for the study groups (data not shown). Cumulative overall survival did not differ between the two groups (P=0.67, fig 2⇓). After 10 years of follow-up, the overall survival rate among women with interval cancers was 72.6% (68.5% to 76.3%) and among women with cancers in the non-screened group was 68.9% (67.3% to 70.5%).

Table 3⇓ shows data derived from Cox proportional hazards model analyses of age at diagnosis and time since last normal screening result as possible determinants of a difference in survival between the cancer groups. Breast cancer specific mortality did not differ between the interval cancer group and the non-screened cancer group (hazard ratio 0.98, 95% confidence interval 0.84 to 1.15, P=0.81). There was no association between time since last normal screening result and survival (table 3). The results did not change after adjustment for age at diagnosis, year of diagnosis, and county of residency (data not shown).

A secondary analysis restricted to interval cancers and stratified by screening round showed no evidence that survival was associated with screening round, either overall or after stratification by time since last normal screening result (table 4⇓). Furthermore, after up to four screening rounds, the incidence of interval cancers was not associated with number of screening rounds. When the analysis was restricted to counties with a minimum of two years and two months of follow-up after examination, the incidence per 100 000 woman years was 163.4 in the first screening round, 162.5 in the second, 193.3 in the third, and 166.5 in the fourth.

Discussion

The survival of women with a diagnosis of interval breast cancer after a normal mammogram is similar to that of women with breast cancer diagnosed before an invitation to a breast cancer screening programme. Contrary to our a priori hypothesis, we found no evidence that tumours that become clinically evident shortly after the last normal screening result were more aggressive in terms of larger size, higher grade, higher proportion of node metastases, or lower survival than non-screen detected breast cancers. Among the interval cancers, average tumour size increased slightly over time since last normal screening result, but no other characteristics of the tumour or risk of dying from breast cancer varied by time since the last normal screening result.

Although several investigators have examined whether interval cancers are associated with poor survival, controversy remains. Previous studies have been limited by small sample size[7-10 20 24-27]; invalid comparison groups, notably screen detected cancers[9 25-27]; or use of historical controls.[8 11 12] Furthermore, the findings in these studies were inconsistent. Analysis based on randomised trials of mammography screening found that survival with interval cancers was similar,[7 27] better,[20] or poorer[24] than survival with non-screen detected cancers. Although studies based on randomised trials have a valid comparison group, chance could explain the inconsistent findings because the sample sizes in all the studies were limited (<100 interval cancers).[7 20 24 28]

In observational studies, where survival rates of women with interval cancers are compared with those of women with screen detected cancers or historical controls, or both, survival associated with interval cancers was similar to that of non-screen detected cancers in some studies,[9 11 26] worse in others,[14] and worse than screen detected cancers but better than clinically detected cancers in studies where interval cancers were compared with both screen detected and historical controls.[10 12 14 20] However, in these studies comparisons are likely to be confounded by lead time, overdiagnosis, and temporal trends in survival from breast cancer.[4 5 11] The only remaining alternative is contemporary patients unaffected by mammography screening. Theoretically, the ideal comparison group would be breast cancer diagnosed among unscreened women who would have attended screening if they had been invited. Such a design would eliminate the potential confounding by factors that affect both attendance and outcome. However such a study is not feasible; to our knowledge there is limited reason in the Norwegian healthcare system to believe in any substantial bias through this mechanism, and this bias, if it exists, would affect only a small proportion of incident breast cancers because the attendance rate in the Norwegian mammography screening programme is high (77% among invited women). Overall survival was similar between women

with interval cancers and those with non-screen detected cancers (fig 2), indicating that the results were not influenced by the potential selection bias among women with interval cancer.

Strengths and limitations of this study

To date, this population based study is the largest in the area of interval breast cancer and has the longest follow-up. The staggered introduction of the screening programme and the comparison of interval cancers with non-screen detected breast cancer avoided major biases.

This study, however, has several potential limitations. Because only a few of the interval cancers had been individually reviewed, we were unable to distinguish true interval cancers from those overlooked when the mammograms were examined. In a previous review in Norway comprising around 200 interval cancers, 35% were reinterpreted as overlooked, 23% showed minimal signs of malignancy, and 42% were true interval cancers,[29 30] similar to the results of other studies.[31 32] The overlooked tumours were on average larger and more often node positive than the true interval cancers. This could be because the affected women were reassured by the last normal mammogram result and therefore delayed seeking medical care. However, other studies have found no differences in survival between interval cancers classified as true or overlooked.[33 34]

In each Norwegian county, introduction of the breast cancer screening programme was preceded by the establishment of specialised multidisciplinary teams.[4 13] The goal of these teams was to provide the best possible management of all women with newly diagnosed breast cancers in the county, regardless of whether the cancer was diagnosed by mammography screening. We have shown previously that this optimised management entailed a substantial reduction in mortality also among women with breast cancer not diagnosed by mammography screening.[4 13] Owing to the design of our current study, only women with interval cancers were managed by multidisciplinary teams. Hence it is conceivable that better treatment eliminated altogether a poorer prognosis among the women with interval cancers than among those with non-screen detected cancers. The possible influence of such confounding could not be tested in our study because it would have required more detailed individual data on prognostic factors, treatment, and overall management. However, the similar proportion of women in each group who received adjuvant tamoxifen treatments provides some reassurance against a major confounding.

Conclusions

We conclude that tumours associated with interval breast cancers are more likely to be larger than those diagnosed in the absence of mammography screening; but they have strikingly similar survival outcomes. Furthermore, the characteristics of the tumours (except for an increase of 2.2 mm in diameter) and the prognosis of women with interval cancers were not associated with time since last mammography. These findings challenge the theory of a strong correlation between growth rate and metastatic behaviour. Our study provides no compelling support for more aggressive primary treatment of interval breast cancers than non-screen detected cancers with similar prognostic features.[14]

Contributors: MK designed the study and did the statistical analysis. MK had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MK, RT, MB, and HOA interpreted the data and cowrote and edited the paper.

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Ethical approval: The research protocol was approved by the Norwegian Social Science Data Services 2008. Individual informed consent was not requested.

Data sharing: No additional data available.

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What is already known on this topic

Previous randomised trials on mammography screening found that interval breast cancers were associated with similar, better, or poorer survival compared with non-screened breast cancers

These inconsistent findings can be explained by small sample sizes (<100 interval cancers)

Observational studies suggested that interval cancers were associated with poor survival but were limited by small sample size and invalid comparison groups

What this study adds

Interval breast cancers were more likely to be larger than breast cancers diagnosed in the absence of mammography screening

Survival outcomes between the two cancer groups were, however, strikingly similar

Our study provides no compelling support for more aggressive primary treatment of interval breast cancers than non-screening cancers with similar prognostic features

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Tables

Table 1| Characteristics of women with breast cancer in interval cancer group and in non-screened cancer group. Values are numbers (percentages) unless stated otherwise

Characteristics	Interval cancer group (n=1816)	Non-screened cancer group (n=5300)	P value
Mean (SD) age at diagnosis (years)	59.4 (5.7)	60.1 (7.1)	
Histological type:			
Ductal	1377 (75.8)	4176 (78.8)	<0.001
Lobular	245 (13.5)	531 (10.0)	
Other	194 (10.7)	593 (11.2)	
Tumour size*:			
1 (<20 mm)	962 (56.1)	2464 (59.9)	<0.001
2 (>20-50 mm)	574 (33.5)	1344 (32.7)	
3 (>50 mm)	137 (8.0)	106 (2.6)	
4 (ingrowth)	42 (2.5)	197 (4.8)	
Unknown	101 (5.6)†	1189 (22.4)†	
Nodal status*:			
Positive	910 (54.4)	2805 (58.7)	<0.001
Negative	764 (45.6)	2491 (41.3)	
Missing	142 (7.8)†	520 (9.8)†	
Stage‡:			
I	750 (41.5)	2607 (49.4)	<0.001
II	913 (50.6)	2236 (42.4)	
III	56 (3.1)	153 (2.9)	
IV	87 (4.8)	279 (5.3)	
Sentinel node biopsy	869 (47.9)	798 (15.0)	<0.001
Tamoxifen administered	701 (38.6)	1912 (36.1)	<0.001
Total No of deaths	246 (13.5)	1307 (24.7)	<0.001
Deaths from breast cancer	194 (10.7)	979 (18.5)	<0.001

*Based on pathological tumour, node, and metastasis classification.[21]

†% of total breast cancers.

‡I, localised breast cancer; II, lymph node positive; III, growth into skin or chest wall; and IV, metastasis. Missing information on stage: 10 interval cancers and 25 non-screened cancers.

Table 2| Tumour characteristics of interval breast cancers in six month intervals from last normal screening result to diagnoses. Values are numbers (percentages) unless stated otherwise

	Time since last normal screening result (months)			
Characteristics	**0-6 (n=181)**	**7-12 (n=497)**	**13-18 (n=554)**	**19-24 (n=584)**
Mean (SD) tumour size (mm)	19.3 (12.2)	19.8 (11.8)	20.6 (12.5)	21.5 (13.4)
Node negative	86 (52.1)	253 (54.5)	267 (52.8)	304 (56.4)
Missing node status*	16 (8.8)	33 (6.6)	48 (8.7)	45 (7.7)
Grade I	35 (24.0)	81 (19.6)	92 (20.2)	130 (27.0)
Grade II	67 (45.9)	206 (49.9)	214 (46.9)	213 (44.3)
Grade III	44 (30.1)	126 (30.5)	150 (32.9)	138 (28.7)
Missing grade*	35 (19.3)	84 (16.9)	98 (17.7)	103 (17.6)
Oestrogen receptor status:				
Positive†	92 (74.8)	224 (69.6)	251 (71.7)	245 (73.8)
Negative‡	31 (25.5)	98 (30.4)	99 (28.3)	87 (26.2)
Missing data*	58 (32.0)	175 (35.2)	204 (36.8)	252 (43.2)
Progesterone receptor status:				
Positive†	64 (52.9)	162 (51.1)	181 (53.2)	174 (53.2)
Negative‡	57 (47.1)	155 (48.9)	159 (46.8)	153 (46.8)
Missing data*	60 (33.2)	180 (36.2)	214 (38.6)	257 (44.0)

*% of total breast cancers.
†≥10% positive staining.[21]
‡<10% positive staining.[21]

Table 3| Hazard ratios (95% confidence intervals) for breast cancer specific mortality between breast cancer groups overall and across age categories

			Age at diagnosis (years)							
	Overall		50-54		55-59		60-64		65-72	
Variables	Hazard ratio* (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Non-screened cancer group	1 (reference) (n=5300 cancers)		1 (reference) (n=1507 cancers)		1 (reference) (n=1558 cancers)		1 (reference) (n=963 cancers)		1 (reference) (n=1672 cancers)	—
Interval cancer† group	0.98 (0.84 to 1.15) (n=1816 cancers)	0.81	0.81 (0.57 to 1.16) (n=429 cancers)	0.25	1.13 (0.86 to 1.49) (n=578 cancers)	0.37	0.89 (0.61 to 1.30) (n=399 cancers)	0.55	1.02 (0.76 to 1.37) (n=410 cancers)	0.89
Months since last screen:										
0-6	1.09 (0.70 to 1.67)	0.53‡	0.68 (0.28 to 1.65)	0.61‡	1.61 (0.80 to 3.29)	0.84‡	1.19 (0.44 to 3.21)	0.78‡	1.12 (0.42 to 3.00)	0.91‡
7-12	0.97 (0.74 to 1.28)		0.81 (0.43 to 1.53)		1.19 (0.77 to 1.85)		0.82 (0.42 to 1.60)		0.97 (0.56 to 1.69)	
13-18	1.06 (0.82 to 1.36)		1.00 (0.58 to 1.76)		1.04 (0.67 to 1.64)		1.37 (0.72 to 2.09)		1.01 (0.62 to 1.68)	
19-26	0.87 (0.66 to 1.15)		0.66 (0.31 to 1.40)		1.04 (0.66 to 1.65)		0.52 (0.23 to 1.19)		1.04 (0.66 to 1.63)	

*Age adjusted.

†Categorised as time since last normal mammogram (time since last screen) in six month intervals.

‡P for trend.

Table 4| **Age adjusted hazard ratios (95% confidence intervals) for breast cancer specific mortality among women with interval breast cancers comparing screening round according to time since last normal screening result**

		Time since last normal screening result (months)				
Screening round (No of cancers)	**Overall**	**0-6**	**7-12**	**13-18**	**19-24**	**P for trend**
1 (n=564)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	0.41
2 (n=475)	0.89 (0.63 to 1.27)	0.85 (0.28 to 2·64)	1.06 (0.55 to 2.06)	0.55 (0.29 to 1.02)	1.48 (0.76 to 2.87)	0.72
3 (n=355)	0.86 (0.58 to 1.27)	1.07 (0.36 to 3·23)	1.18 (0.58 to 2.41)	0.39 (0.17 to 0.89)	1.18 (0.54 to 2.60)	0.85
4 (n=220)	0.69 (0.39 to 1.21)	0.32 (0.04 to 2·61)	0.66 (0.22 to 1.94)	0.43 (0.15 to 1.23)	1.65 (0.64 to 4.29)	0.74
5 (n=182)	0.99 (0.42 to 2.31)	1.19 (0.37 to 9·88)	0.38 (0.05 to 2.93)	1.39 (0.40 to 4.80)	—	0.17

Figures

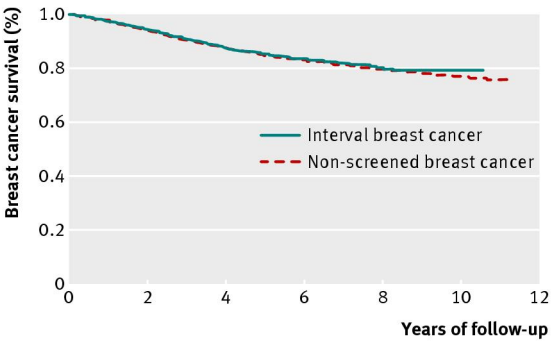

Fig 1 Cumulative breast cancer survival plot for women with breast cancer by group

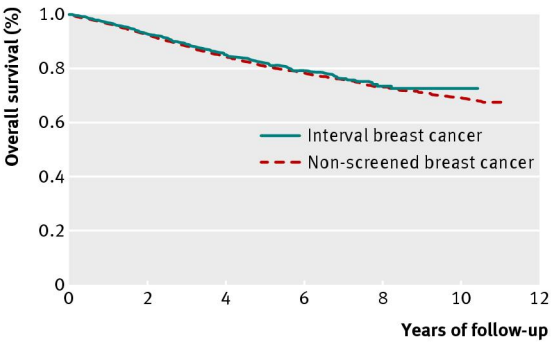

Fig 2 Cumulative overall survival plot for women with breast cancer by group